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PROTEIN-LOSING ENTEROPATHY

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During the past few years the availability of isotopically labeled proteins has led to significant advances in understanding the role of the gastrointestinal tract in the homeostasis of plasma proteins in both normal and pathological states. The gastrointestinal tract has been shown to play a significant role in the synthesis of serum proteins, including the immunoglobulins and lipoproteins,[1] in the absorption of intact γ-globulin in newborn animals[2] and in the degradation of the plasma proteins. A major development has been the demonstration that loss of serum proteins into the gastrointestinal tract plays a part in their normal degradation and that excessive gastrointestinal protein loss is a major cause of hypoproteinemia seen in association with a variety of disorders. When serum proteins are lost into the gastrointestinal tract, they are catabolized rapidly into their constituent amino acids which are reabsorbed and made available to the body for resynthesis of protein. Hypoproteinemia develops when the rate of protein catabolism exceeds the body's protein synthetic capacities. The study of gastrointestinal protein loss has been of significance to the gastroenterologist in a number of ways. It has provided a better understanding of the pathogenesis of the hypoproteinemia seen in association with gastrointestinal diseases. The techniques for quantitation of gastrointestinal protein loss have also been of value in determining the site of disease in the intestinal tract, determining the degree of activity of the gastrointestinal disease, and in studying the efficacy of therapy of some intestinal disorders. The discovery of a number of new clinical syndromes involving protein loss into the gastrointestinal tract has been a development of special importance in the past few years. Gastrointestinal protein loss has been reviewed previously in 1962[3, 4] and 1963.[5]

In the present report recent developments in the methods for quantitation of gastrointestinal protein loss and the recently described syndromes involving gastrointestinal protein loss will be reviewed.

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Techniques for the Quantitation of Gastrointestinal Protein Loss

A wide variety of techniques have been proposed for the detection and quantitation of gastrointestinal plasma protein loss including metabolic balance studies,[6] detection of plasma proteins in the gastrointestinal secretions by electrophoretic and immunological methods,[7-10] and the use of intravenously administered radioactively labeled macromolecules including iodinated serum proteins,[7, 10, 11] iodinated polyvinylpyrrolidone,[12] chromium^{51}-labeled proteins,[13] and copper^{67}-labeled ceruloplasmin.[14] Although each of these techniques has been of great value, each has significant limitations. Frequently, a combination of two of the techniques is required for a full understanding of the protein metabolism.

Nitrogen Balance Techniques

In 1949 Albright and co-workers[6] described a complex nitrogen, calcium, and

phosphorus metabolic balance technique to study the fate of intravenously administered unlabeled human serum albumin. Through the use of this ingenious but laborious technique they were able to demonstrate for the first time that idiopathic hypoalbuminemia could be caused by excessive protein catabolism rather than defective protein synthesis. Subsequent studies have shown that spuriously normal values for protein catabolism may be obtained using this technique in some patients with severe gastrointestinal protein loss.[15] Moreover, this metabolic balance technique cannot indicate the site of albumin catabolism and thus cannot be used to quantitate gastrointestinal albumin loss.

Direct Demonstration of Serum Proteins in the Gastrointestinal Secretions

Serum proteins have been identified in the gastrointestinal secretions by electrophoretic, immunological, and immunoelectrophoretic methods. Citrin et al.[7] demonstrated albumin in the gastric secretions of a patient with giant rugal hypertrophy using paper electrophoresis. Steinfeld et al.[10] similarly demonstrated albumin in the secretions of the small intestine of patients with regional enteritis using immunological techniques. Subsequently, it has been shown that the serum proteins may be demonstrated in the gastrointestinal secretions of normal subjects if the activity of the intestinal proteolytic enzymes is inhibited. Holman et al.[9] and Gullberg and Olhagen[8] demonstrated albumin and γ-globulin in the gastric and salivary fluids of normal subjects using the Ouchterlony immunological technique and paper electrophoresis. Subsequently, albumin and γ-globulin have been demonstrated by others using paper electrophoresis and the Ouchterlony technique and immunoelectrophoresis in the salivary, gastric, duodenal, ileal, and biliary fluids of normal subjects.[16-21] Using the Ouchterlony technique, Barandun, Nussle, Riva and their associates[18, 22, 23] have demonstrated prealbumin, albumin, siderophilin, α_2-macroglobin, fibrinogen, and γ-globulin in the gastric and small intestinal fluids of adults and children as well as in the meconium and feces of infants. Although these techniques of direct demonstration of serum proteins in the secretions of the intestinal lumen have been of value in the detection of gastrointestinal protein loss associated with some conditions such as gastric carcinoma,[17, 24] gastric rugal hypertrophy,[7, 17, 25, 26] ulcerative colitis,[19] and idiopathic hypoproteinemia,[18, 27-29] the techniques have not been satisfactory for the quantitation of gastrointestinal protein loss since all the gastrointestinal secretions cannot be aspirated quantitatively.

Radio-Labeled Macromolecules

A number of techniques using radio-labeled macromolecules have been introduced in an attempt to quantitate gastrointestinal protein loss. An ideal radio-label for the detection of gastrointestinal protein loss should fulfill the following requirements: (a) The labeled serum protein should have a normal metabolic behavior, thus permitting the simultaneous determination of rates of endogenous protein catabolism, protein synthesis, and intestinal protein loss. (b) There should be no absorption of the label from the intestinal tract after catabolism of the protein since this would result in an underestimation of the extent of the gastrointestinal protein loss. (c) There should be no excretion of the label into the gastrointestinal tract except when bound to protein. Such secretion of label in the salivary, gastric, or biliary fluids would result in overestimation of the magnitude of the gastrointestinal protein loss and would make determination of the site of the loss impossible. None of the presently available labeled macromolecules completely fulfills all requirements.

I^{131}-Labeled Serum Proteins

The first widely used radioactive macromolecules, radioiodinated serum proteins, do fulfill the first requirement. That is, the serum proteins can be iodinated without altering their metabolism or distribution in the body if care is taken to avoid damage due to self-irradiation and to control the degree of iodination.[30-31] Using intravenously administered iodinated albumin, one may determine by dilution the plasma volume and the total body albumin pools.

From the decline in radioactivity in the serum and whole body the rate of albumin degradation and in the steady state the rate of albumin synthesis can be determined (fig. 1). Patients with gastrointestinal protein loss have reduced circulating and total body pool of albumin, a normal or slightly increased rate of albumin synthesis, and a markedly shortened albumin survival.[5, 9-11, 32] Although iodinated proteins have been very valuable in the study of protein metabolism in patients with gastrointestinal protein loss they have certain limitations. There is rapid reabsorption of the radioiodide label following the catabolism of the labeled protein in the intestinal lumen and there is active secretion of radioiodide into the intestinal lumen, in the salivary, gastric, and certain small intestinal secretions. The analysis of the data obtained from the serum and urinary radioactivity curves thus shows that hypercatabolism is the cause of the hypoproteinemia but does not implicate the gastrointestinal tract as the site of this apparent hypercatabolism of albumin.

The fecal output of I^{131} following intravenous injection of I^{131}-proteins cannot be used to give an accurate quantitative estimate of gastrointestinal protein loss since most of the radio-label entering the gastrointestinal tract is reabsorbed and excreted in the urine. The determination of fecal radioiodine has, however, been shown to be of value as a qualitative test for the detection of excessive gastrointestinal protein loss. In the studies of Steinfeld et al.[10] normal subjects excreted less than 0.04% of the body content of radioiodine in the stool each day following intravenous I^{131}-albumin administration while patients with active regional enteritis and ulcerative colitis excreted from 0.1 to 1.6% of the body content of radioactivity each day in the stools. Comparable high rates of fecal excretion of radioiodine were found in patients with protein-losing enteropathy by Jarnum[33] and Waldmann et al.[32] There was, however, no significant correlation between the quantity of radioactivity excreted in the feces and the serum albumin concentration or the albumin life-span. Patients with diarrhea or those with lesions low in the gastrointestinal tract or subjects with pancreatitis and maldigestion of protein had a much higher fecal excretion of radioactivity than might be expected on the basis of other techniques for quantitating gastrointestinal protein loss.

In an effort to overcome the problem of reabsorption of the radioiodide label, Citrin et al.[7] used intubation to collect the gastric secretions from a patient with giant gastric rugae who had previously received iodinated albumin intravenously. Sufficient protein-bound radioiodine was identified in the gastric secretions to explain the hypercatabolism of albumin seen in this patient. Iodinated serum proteins used in conjunction with intubation have similarly been used to demonstrate small intestinal protein loss by Holman et al.[9] and by a number of investigators to study the role of the normal gastrointestinal tract in serum protein metabolism.[16, 34, 36] This technique has not had wide use in disease since one cannot collect all the gastrointestinal secretions especially those associated with lesions in the small and large intestines and since the intubation procedure itself may traumatize the bowel leading to transient protein loss.

Jeejeebhoy and Coghill[37] have attempted to solve the problem involved in the rapid catabolism of iodinated albumin in the gastrointestinal tract and the reabsorption of the radio-label by administering an ion exchange resin (amberlite IRA-400) orally at 4-hr intervals during the period of the intravenous iodinated albumin turnover study. Theoretically, any iodinated albumin lost into the gastrointestinal tract would be catabolized and the radioiodine released would be quantitatively attached to the resin and excreted in the feces. When I^{131}-albumin was fed orally simultaneously with the administration of the ion exchange resin from 70 to 80% of the administered radioactivity was recovered in the feces.[37] Unfortunately, one of the requirements for a suitable test substance has not been met by this technique, namely, that there be no secretion of nonprotein-bound radioiodide into the intestinal tract. Following intravenous administration of sodium radioiodide up to 50% of the administered radioactivity was excreted bound to the resin in

the feces.[38-41] Because of this secretion of radioiodide into the gastrointestinal lumen, in the salivary and gastric secretions, one cannot differentiate catabolism of proteins at other body sites from gastrointestinal protein loss. In addition, the resin did not trap all radioiodine liberated in the bowel, since only 35% of the radioactivity of orally administered iodinated albumin given between doses of resin was excreted in the stool with the remaining 65% being excreted in the urine.[40] Thus this technique does not provide any information that is not available using iodinated albumin turnover data alone and cannot be used to quantitate accurately gastrointestinal protein loss.

I^{131}-Labeled Polyvinylpyrrolidone (I^{131}-PVP)

The difficulties inherent in the use of I^{131}-labeled proteins led to the development by Gordon[12] of an indirect means of demonstrating gastrointestinal protein loss, the use of intravenously administered iodinated polyvinylpyrrolidone (PVP). I^{131}-PVP is a synthetic polymer, with an average molecular weight of 40,000, that is unaffected by the digestive enzymes and is poorly absorbed from the gastrointestinal tract. To perform the PVP test 10 to 25 μc were injected intravenously and the radioactivity appearing in the subsequent 4 days was determined. Control subjects excreted 0 to 1.5% of the intravenously administered dose of radioactivity into the stools while patients with excessive gastrointestinal protein loss excreted from 2.9 to 32.5% of the administered dose into the stools.[12, 42] These findings have been confirmed by a large number of laboratories.[11, 22, 43-46] Neither hypoproteinemia per se nor diarrhea alone caused false positive tests. Gordon et al.[42] Jarnum,[45] and Dawson et al.[46] have found that there is a close correlation between the fecal PVP excretion and the serum albumin concentration in patients with idiopathic hypercatabolic hypoproteinemia and that the PVP excretion roughly parallels the severity of the enteric protein loss. In contrast to these findings, Parkins,[47] studying

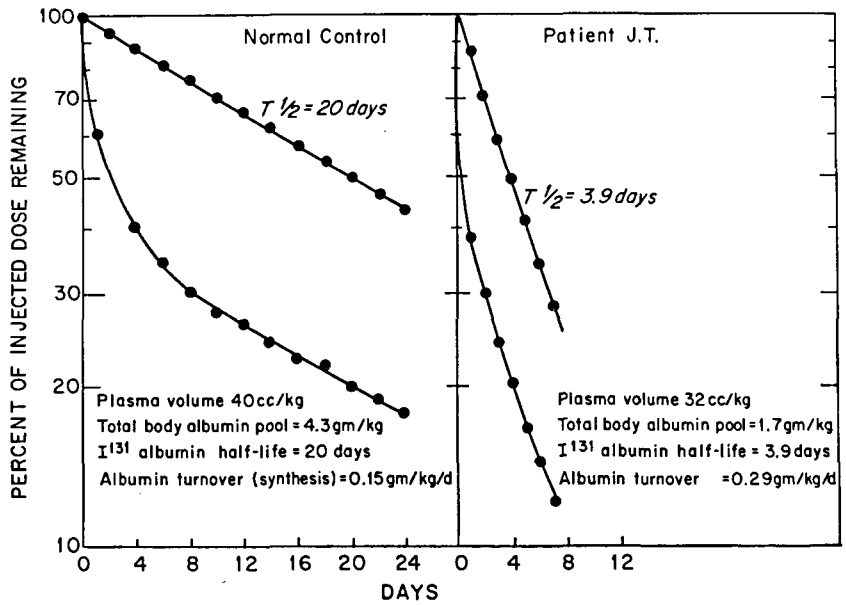

FIG. 1. The turnover of I^{131}-albumin in a normal subject and in a patient, J. T., with gastrointestinal protein loss secondary to intestinal lymphangiectasia. The *upper curves* represent the decline in total body radioactivity with time. The *lower curves* represent the decline in plasma radioactivity. The total body albumin pool was markedly reduced in patient J. T. The survival half-life of iodinated albumin was markedly shortened and the albumin synthetic rate was slightly greater than normal.

patients with nontropical sprue, found that the fecal PVP excretion did not correlate either with the severity of the disease or with the serum protein concentration. A possible explanation of these latter findings is that the serum albumin level reflects the balance between synthesis and degradation or loss over a period of many days and the PVP test serves only as an index of the protein loss on the day of injection. Thus it would not correlate with the serum albumin concentration if there were a variable rate of loss into the gastrointestinal tract or if there were a decrease in the rate of albumin synthesis.[48]

Although the I^{131}-PVP test provides a simple procedure for the detection of enteric protein loss, there are certain limiting factors in its use. A few patients have had side effects following intravenous administration of this substance including chest and back pain, flushing, and unconsciousness.[45] The PVP molecule is not a normal mammalian metabolite substance and differs in size, charge, distribution, and survival from the serum proteins. It is only thus by inference that one can get information on serum protein metabolism with its use. I^{131}-PVP is very rapidly cleared from the serum by the reticuloendothelial system and the kidney with half-times of disappearance ranging from 8 hr to 3 days.[45, 49, 50] Ravin et al.[51] showed that the rate of PVP clearance is variable depending on the size of macromolecule particles. The PVP preparations available have all been heterogeneous in size and have had variations from batch to batch in urinary clearance, blood disappearance, and fecal excretion. In all cases there were marked differences in the metabolic behavior of PVP from that of the iodinated albumin and γ-globulin preparations.

The PVP iodine bond has been shown to be relatively unstable both on standing, in vitro,[45, 52] and in slightly alkaline media.[53] The instability of the bond in alkaline media suggests that radioiodine may be released from the PVP in the presence of the alkaline small bowel secretions. Significant and variable quantities of the radioactivity from I^{131}-PVP entering the gastrointestinal tract are reabsorbed. On oral administration Gordon[12] found approximately 90% of the dose appearing in the subsequent stool collections. Subsequent studies using different preparations have found greater absorption with from 17 to 60% of the orally administered PVP absorbed.[45, 46, 54] Finally, there is normally some secretion of PVP into the bile making it difficult to use the substance to determine the site of enteric protein loss.[55] Yet despite these limitations I^{131}-PVP has proved of great value as a screening test for excessive gastrointestinal protein loss.

Cr^{51}-Labeled Albumin

Human serum albumin labeled with chromium[51] appears to have a number of valuable characteristics for the study of intestinal protein loss.[13] $Cr^{51}Cl_3$ has been used to label a number of serum proteins;[56] however, only Cr^{51}-albumin has been used widely in the study of enteric protein loss. The Cr^{51} label is neither significantly absorbed from nor secreted into the gastrointestinal tract. From 93 to 100% of the radioactivity of an orally administered dose of Cr^{51}-albumin appeared in the subsequent fecal collections.[13, 39, 57] Following intravenous administration of Cr^{51}-albumin, normal subjects excreted from 0.1 to 0.7% of the administered radioactivity in the stools over the subsequent 4-day period.[13] Patients with enteric protein loss excreted a greater amount, from 2 to 40%, of the administered dose during this period.[13, 39] In the 40 subjects with gastrointestinal protein loss studied, there was a close correlation between the fecal Cr^{51} excretion and the fractional catabolic rate of I^{131}-albumin and in inverse correlation between the fecal Cr^{51}-albumin excretion and the serum albumin concentration.[39] No false negative or false positive values were found in over 200 studies using Cr^{51}-albumin. False positive results could occur, however, if there were urinary contamination of the stool during the first 24 hr, since significant chromium is excreted in the urine during this period.

A more meaningful quantitation of enteric protein loss may be obtained if the fecal excretion of Cr^{51} is related to the serum radioactivity curve comparable to the technique for quantitative gastrointestinal red

cell loss.[39] The stools are collected daily from the time of injection and the stool radioactivity is related to the corresponding plasma radioactivity for that day. The data may be expressed as the fraction of the plasma pool or as the milliliters of plasma lost in the gastrointestinal tract per day. The milliliters of plasma cleared into the gastrointestinal tract per day may be determined from:

> The amount of plasma albumin lost per day = radioactivity in the stool in the period/mean radioactivity in the serum in the period.

The mean clearance values for the days 2 through 12 after administration of the isotope are used. Normal subjects cleared the albumin from 5 to 25 ml of plasma, representing less than 1% of the total plasma albumin pool per day into the intestinal tract.[39] Patients with protein-losing enteropathy cleared albumin equivalent to that in 180 to 1800 ml of plasma per day, representing from 10 to over 50% of the plasma pool each day (fig. 2). Intravenously administered chromium^{51}-albumin may be used in conjunction with oral intubation to successfully determine the site of enteric protein loss.[13]

Despite its advantages, chromium^{51}-albumin has significant limitations. Only 90 to 96% of the preparation was precipitable by perchloric or phosphotungstic acid. In addition a small percentage of the labeled molecules tend to form dimers.[36] Of more serious import is that chromium albumin has a short apparent half-life of survival in man of about 3 to 10 days in contrast to iodinated albumin which has a half-life of 14 to 22 days.[36, 39, 57] This short apparent half-life of chromium albumin has been shown to be due to elution of the chromium from the protein in experiments using proteins doubly labeled with I^{125} and chromium^{51} (T. A. Waldmann, *unpublished observations*). Because of this elution of the chromium comparable to that seen with chromium-labeled red cells, chromium^{51}-labeled albumin cannot be used to determine the pool sizes of the serum proteins or the rates of protein synthesis and catabolism.

Intravenous administration of $Cr^{51}Cl_3$ with the in vivo labeling of a number of serum proteins has been used successfully to detect gastrointestinal protein loss.[57, 50] However, with this procedure a significant fraction of the administered radioactivity is rapidly cleared by the kidney and the reticuloendothelium system and the apparent protein survival is even shorter than with the use of chromium^{51}-labeled albumin.[57] Recent studies indicating that chromium is tightly bound to transferrin[58] suggest that chromium-labeled transferrin might be of value in future studies of enteric protein loss.

Copper^{67}-Labeled Ceruloplasmin

Intravenously administered copper^{67}-labeled ceruloplasmin has been shown to fulfill the major requirements for a technique for quantitation of gastrointestinal protein loss in studies in dogs and man.[14] Following oral administration of copper^{67}-labeled ceruloplasmin to rats, dogs, and men, from 80 to 100% of the orally administered radioactivity appeared in the stools, indicating that absorption of the radiocopper moiety of copper-labeled ceruloplasmin is minimal. The metabolism of intravenously administered copper^{67}-labeled ceruloplasmin was found to be quite comparable to that of I^{131}-labeled ceruloplasmin,[14] in accordance with previous observations indicating that exchange labeling of ceruloplasmin with copper^{67} did not alter significantly the metabolism of this protein and that the copper^{67} is an integral part of the protein throughout the life of the molecule.[59] It was found that approximately 20% of the circulating ceruloplasmin pool in dogs and in normal man was catabolized per day. Two per cent of the circulating pool of copper^{67} ceruloplasmin was excreted into the stool daily in normal subjects.[14] The gastrointestinal loss normally accounted for only about 10% of the over-all catabolism of ceruloplasmin. In patients with excessive gastrointestinal protein loss 17 to 45% of the circulating pool of copper^{67} ceruloplasmin was lost into the gastrointestinal tract each day representing from 54 to nearly 100% of the over-all metabolism of this

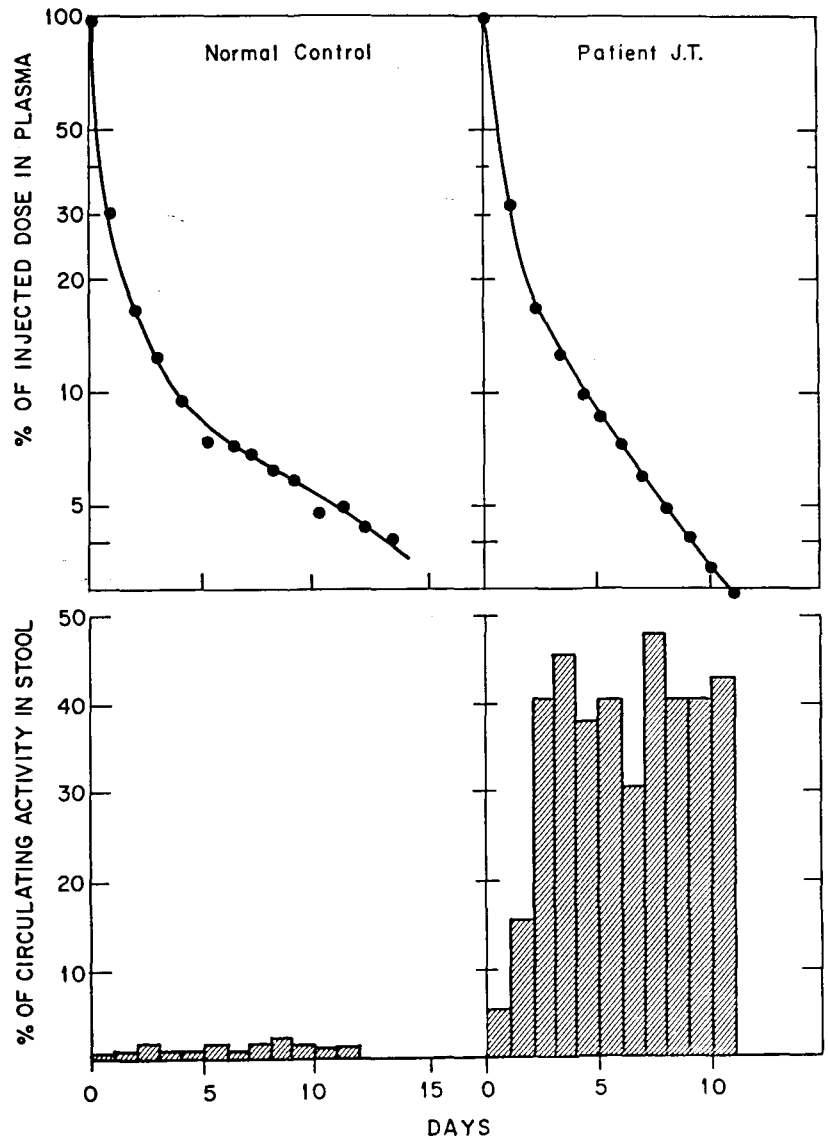

FIG. 2. The fecal clearance of chromium[51] following intravenous chromium[51]-albumin in a normal subject and a patient, J. T., with gastrointestinal protein loss. The normal subject cleared 0.8% of the plasma pool of labeled albumin into the gastrointestinal tract each day, while patient J. T. cleared over 30% of the plasma pool into the gastrointestinal tract each day, indicating severe gastrointestinal protein loss.

protein in these subjects. Although copper[67]-labeled ceruloplasmin fulfills the major criteria for an adequate label for the quantitation of gastrointestinal protein loss, the preparation of the copper[67] is difficult and expensive, but in situations where other techniques give conflicting results as in the determination of the role of the normal gastrointestinal tract in plasma protein metabolism, copper[67] is of value.

Although Cr^{51}-albumin, I^{131}-PVP, and I^{131}-albumin are adequate as screening procedures for the routine diagnosis of gastrointestinal protein loss, none of these pro-

cedures is entirely satisfactory. A more complete analysis of the protein metabolism may be achieved through the simultaneous use of Cr^{51}-labeled albumin and I^{125}-albumin. The size of the albumin pools and rates of albumin catabolism and synthesis may be determined from the I^{125}-albumin data and the rate of albumin loss into the gastrointestinal tract roughly quantitated with the Cr^{51}-albumin.

Physiology and Pathophysiology

Recently, considerable attention has been directed toward determining the anatomical site of catabolism of the serum proteins. Kinetic analysis of studies of the degradation of I^{131}-albumin and γ-globulin in man suggests that the site of catabolism is a compartment in rapid equilibrium with the plasma protein pool.[60, 61] As discussed above albumin, γ-globulin, and the other serum proteins have been demonstrated in the gastrointestinal secretions of normal subjects by electrophoretic and immunological techniques. Thus the gastrointestinal tract has been shown to play a role in the physiological degradation of the serum proteins. The magnitude of this process has, however, been the subject of considerable controversy. Wetterfors et al.[16, 36] determined the quantity of protein-bound radioactivity in the buffered gastric and jejunal secretions aspirated from normal subjects who had received intravenous iodinated albumin. They estimated that from 1.4 to 4 g of albumin, representing 10 to 30% of the normal catabolism, were lost into the stomach each day and that from 4 to 6 g, representing from 30 to 50% of the normal albumin catabolism, were lost into the small bowel each day. By comparable methods Glenert et al.[34] estimated that 50 to 60% of albumin degradation in the dog was due to gastrointestinal loss. Armstrong et al.,[62] studying the isolated gut segments of rabbits, and Campbell et al.,[63] studying the secretions in isolated segments of the small intestine of sheep following intravenous I^{131}-albumin administration, also concluded that the gastrointestinal tract was a major site of serum protein degradation. Andersen et al.,[35] using similar techniques, found that approximately 38% of the catabolism of γ-globulin in dogs was due to intestinal protein loss. A major criticism of these techniques is that the study periods were very short relative to the life-span of the serum protein and that only a small segment of the intestinal tract was studied at a time. Thus minor trauma to the intestinal mucosa during the intubation and surgical procedures resulting in the loss of only one or two drops of plasma or lymph during the study period would have given these high values for gastrointestinal catabolism of serum proteins. Other studies suggest that the normal gastrointestinal tract plays a less significant role in the catabolism of serum proteins. The removal of the subdiaphragmatic gastrointestinal tract of rabbits, rats, and mice resulted in only a 0 to 10% prolongation of the survival of iodinated albumin in studies by three groups.[64-66] Using chromium^{51}-labeled albumin clearance studies in man, less than 20% of the normal turnover of albumin could be accounted for by enteric protein loss.[39] Using copper^{67}-labeled ceruloplasmin in dogs and man, less than 20% of the daily turnover of ceruloplasmin could be accounted for by gastrointestinal loss of the protein.[14] These studies would suggest that bulk loss of serum, or materials with comparable protein composition, into the gastrointestinal tract is of only minor significance in the normal metabolism of these proteins. It is clear that further work is necessary before the exact magnitude of the gastrointestinal protein loss in normal subjects is understood and before the mechanism of this loss is elucidated.

In patients with diseases affecting the gastrointestinal tract loss of serum proteins into the gastrointestinal tract may increase markedly secondary to obstruction of the gastrointestinal lymphatics with loss of lymph into the intestinal lumen, secondary to exudation through an inflamed or ulcerated mucosa or secondary to a disorder of mucosal cell metabolism. In such patients the half-life of survival of albumin, 7-S-γ-globulin (IgG),[9, 67, 68] γ-macroglobulin (IgM),[69] β-2-A-globulin (IgA), and ceruloplasmin[14] is markedly reduced with an increase in the fraction of the intravascular pool of protein catabolized each day. Nor-

mal subjects catabolize from 5 to 11% of their intravascular pool of albumin or γ-globulin each day. In contrast, patients with gastrointestinal loss may catabolize over 60% of their plasma pool of these proteins each day, with the excess over normal presumably lost into the gastrointestinal tract. In patients with gastrointestinal loss all serum proteins studied including the γ-macroglobulins are lost into the intestinal tract at the same rate irrespective of molecular size.[68, 69] This finding is in contrast with the urinary protein loss in the nephrotic syndrome where smaller serum proteins are lost preferentially and the macroglobulins are lost into the urine only when there is extreme renal damage.[70] In most cases the proteins lost into the gastrointestinal tract are catabolized into their constituent amino acids which are reabsorbed. Hypoproteinemia results when the rate of protein loss and catabolism exceeds the body's capacity to synthesize that protein. The reduction in serum protein concentration is not the same for different proteins. The concentration of albumin and γ-globulin, proteins with the longest normal survival, are most severely depressed. There is usually a less marked depression of the concentration of transferrin, γ-macroglobulin and ceruloplasmin, and normal levels of α_2-macroglobulin and fibrinogen.[5, 71]

The synthetic rate of albumin in patients with gastrointestinal protein loss is normal or increased to a maximum of twice normal.[5, 71] A similar limited capacity to increase albumin synthesis is noted in patients with nephrosis and in normal subjects following plasmaphoresis.[72] The rate of synthesis of the three immunoglobulins (IgG, IgA, IgM) is usually normal in patients with gastrointestinal protein loss when there is no severe inflammatory disease process.[68, 69] Thus, although there can be a marked acceleration of immunoglobulin synthesis following antigenic stimulation, a low plasma concentration does not appear to be an effective stimulus to immunoglobulin production.

The loss of serum components in patients with gastrointestinal protein loss is not limited to the serum proteins. With the use of isotopic techniques it has been shown that iron,[73] copper,[14] calcium,[74] and lipids[75] may also be lost into the gastrointestinal tract. Loss of lymphocytes into the gastrointestinal lumen probably occurs in patients with disordered lymphatic channels since lymphocytopenia is a major feature in patients with intestinal lymphangiectasia,[5] Whipple's disease,[76] regional enteritis, and constrictive pericarditis.[77]

Clinically, hypoproteinemia and edema may be the sole manifestations of the gastrointestinal disease. In other patients growth retardation, the gastrointestinal symptoms, or the symptoms of hypocalcemic tetany may predominate. Iron deficiency anemia, eosinophilia, lymphocytopenia, or aminoaciduria are associated features in occasional patients.

Diseases Associated with Gastrointestinal Protein Loss

Excessive gastrointestinal protein loss is a common phenomenon that has been demonstrated in association with over 40 gastrointestinal disorders (table 1). It has been demonstrated in a significant percentage of patients with active regional enteritis,[10, 46] ulcerative colitis,[10, 22, 46] gastric carcinoma,[17, 24, 36] Whipple's disease,[76] tropical[83] and nontropical sprue,[37, 46, 47, 110] and giant hypertrophy of the gastric mucosa.[7, 11, 26] It is a rare feature in patients with gastrointestinal infections,[3, 87] esophageal and colonic neoplasms,[78] and megacolon.[18,94] It must be emphasized that in many of these patients with clearly defined gastrointestinal tract diseases hypoproteinemia and edema were the only manifestations of the gastrointestinal disorder.

One of the most important recent developments has been the demonstration of gastrointestinal protein loss in association with a variety of generalized diseases and the discovery of a number of new syndromes affecting the gastrointestinal tract. Through these studies, gastrointestinal protein loss has been demonstrated in association with congestive heart failure,[95-98] hypogammaglobulinemia,[9, 22, 44, 100] nephrosis,[22, 101] amyloidosis,[111] and generalized lymphomatosis,[11, 22, 85] as well as the recently described syndromes of intestinal lymphangiectasia,[9, 11, 71, 88] allergic gastroenteropathy,[71, 103]

TABLE 1. *Disorders associated with protein-losing enteropathy*

Disorder	Reference
Esophageal carcinoma	78
Gastric carcinoma	17, 24, 36
Giant hypertrophy of the gastric mucosa	7, 11, 26, 46
Atrophic gastritis	17
Gastric polyp	79
Postgastrectomy syndrome	80–82
Gastrocolic fistula	80
Gluten-induced enteropathy, celiac disease, nontropical sprue	22, 37, 44, 46, 47, 49, 51, 80
Tropical sprue	83, 84
Regional enteritis	3, 10, 11, 22, 46, 52
Whipple's disease	76
Lymphosarcoma of bowel	11, 22, 85
Nonspecific granuloma of bowel	9, 11
Jejunal stenosis	18
Jejunal diverticulosis	46
Chronic gastrointestinal tuberculosis	37, 52, 86
Acute gastrointestinal infection	3, 87
Intestinal lymphangiectasia	9, 11, 18, 32, 71, 75, 88, 89
Tuberous sclerosis with angiomatous malformation of small bowel	90
Fistula between thoracic duct and small bowel	91, 92
Hookworm infection	83
Chronic pancreatitis	91
Kwashiorkor	93
Ulcerative colitis	10, 22, 46
Colonic neoplasm	52, 78
Megacolon	18, 94
Congestive failure, constrictive pericarditis	95–98
Interatrial septal defect	96
Familial myocardiopathy	99
Thrombosis of inferior vena cava	91
Agammaglobulinemia	9, 22, 44, 100
Nephrosis	22, 52, 91, 101
Protein-losing gastroenteropathy associated with angioneurotic edema	102
Allergic gastroenteropathy	71, 103
Acute transient gastrointestinal protein loss	70
Experimental in animals using whole body radiation	104–107
Intraperitoneal nitrogen mustard	104
Experimental nephrosis	108
Experimental pericarditis	109

acute transient gastrointestinal protein loss,[71, 112] and nonspecific granulomatous disease of the bowel.[9, 11]

Congestive Heart Failure

Hypoproteinemia has been described frequently in patients with congestive heart failure, especially in those with constrictive pericarditis.[113, 114] This hypoproteinemia was initially ascribed to defective protein synthesis secondary to liver dysfunction or to dilutional hypoproteinemia associated with an expanded plasma volume or an abnormal distribution of the plasma proteins. In recent years excessive gastrointestinal protein loss has been shown to be a major factor in the hypoproteinemia of 19 patients with congestive heart failure.[91, 95-99, 115-119] Fifteen of these 19 subjects had constrictive pericarditis. In addition, isolated patients have been described with gastrointestinal protein loss associated with generalized myopathy and cardiomegaly, familial myocardiopathy,[99] an interatrial

septal defect,[96] and congenital pulmonic stenosis.[116]

Each of the patients presented with hypoproteinemia and edema as his major clinical features. There was marked hypoalbuminemia and hypogammaglobulinemia with a significant reduction of the total body pools of these proteins. The synthetic rate for albumin was normal while the albumin survival half-time was shortened to less than 4 days.[95, 96, 98, 115, 117, 118] The patients were shown to have excessive gastrointestinal protein loss using I^{131}-PVP- or Cr^{51}-labeled albumin tests.[96, 98, 117]

In addition to the hypoproteinemia the patients had lymphocytopenia and, in one case, hypocalcemic tetany. Despite the extreme gastrointestinal protein loss the symptoms referable to the intestinal tract were only moderate. Diarrhea was present in five of nine patients.[95, 96, 98, 118, 119] Three of the patients also had steatorrhea. The xylose tolerance test was normal when performed.[98] The roentgenograms of the gastrointestinal tract were either normal or showed edema of the small intestinal mucosa.[96, 98, 117] Marked dilation of the submucosal lymphatics of the small bowel[98, 117] comparable to that seen in intestinal lymphangiectasia was demonstrated in two patients.

The mechanism of the protein-losing enteropathy associated with congestive failure has not been fully elucidated. Davidson et al.[96] suggested that the gastrointestinal protein loss was caused by a functional disorder of the intestinal lymphatics secondary to an increase in the central venous pressure. There have been a number of experimental and clinical observations that support this hypothesis. Blalock et al.[120] and Földi et al.[121] have demonstrated marked increases in the thoracic duct pressure and have shown dilation of the lymphatics of the bowel following ligation of the superior vena cava or experimental production of pericarditis in animals. Peterson and coworkers[77, 98] have shown a significant increase in thoracic duct pressure and flow rate in patients with constrictive pericarditis. This increase in thoracic duct pressure and flow is apparently secondary to both a partial obstruction to entry of lymph into the central veins due to high venous pressure and to an increased production of lymph. The patients with constrictive pericarditis have had lymphocytopenia prior to surgery,[77] a feature that has been associated with gastrointestinal loss of lymph. One of the patients with constrictive pericarditis had markedly dilated lymphatics of the superior mediastinum and two had dilated lymphatic channels in the submucosa of the small intestine.[98, 117]

Following pericardectomy, the lymphatic dilation disappeared and the disorders of protein metabolism were completely corrected in seven patients and were markedly ameliorated in the remaining two patients studied.[95, 96, 98, 115, 118]

Gastrointestinal Protein Loss Associated with a Defect in γ-Globulin Synthesis

Holman et al.[9] described a patient with repeated infections, hypogammaglobulinemia, excessive enteric protein loss, and multiple granulomatous ulcers of the terminal ileum and cecum. After resection of the diseased segment the abnormal gastrointestinal protein loss stopped but the serum γ-globulin concentration fell to an even lower level. A number of other cases have subsequently been described with gastrointestinal protein loss associated with defective γ-globulin synthesis.[22, 44, 100, 122] Vesin and co-workers[44] described a patient with hypogammaglobulinemia, protein-losing gastroenteropathy, and malabsorption who responded to treatment with a gluten-free diet with reversal of the steatorrhea and hypoalbuminemia, but with persistence of the extreme hypogammaglobulinemia. The serum albumin concentration was below the lower limit of normal of 3.6 g per 100 ml in 20 of the 24 patients with defective γ-globulin synthesis studied by Waldmann and Laster.[100] Excessive loss of albumin into the gastrointestinal tract was a significant factor in the hypoalbuminemia in three of the six patients of this series studied with I^{131}-albumin and I^{131}-polyvinylpyrrolidone. One of these three patients had a chronic salmonella Newport infection, a second had a spruelike syndrome, and the third had ileocolitis. After treatment of these patients with antibiotics, a gluten-free

diet, and corticosteroids, respectively, there was a complete cessation of the abnormal enteric loss of albumin with a return to normal serum and total body albumin levels. However, the primary defect in γ-globulin synthesis was not affected by this therapy and the hypogammaglobulinemia persisted. It was felt that the primary disorder in these patients was a defect in γ-globulin synthesis that leads secondarily to disorders of the gastrointestinal tract and consequent general enteric loss of the serum proteins.

Gastrointestinal Disease Associated with Nephrosis

In some patients with nephrosis, the reduction in the concentration of the serum proteins was greater than could be explained by the magnitude of the proteinuria. Gitlin et al.[72] and Freeman and Matthews[123] have shown that some such patients, especially children, may have an increase in the fractional catabolic rate of albumin and other serum proteins. Katz et al.[124] have shown that renal catabolism of serum proteins may play a role in this hypercatabolism. Moderate gastrointestinal protein loss also appears to be a factor in this increase in the fractional catabolic rate of serum proteins since abnormal PVP tests have been demonstrated in a significant number of patients with nephrosis by Barandun, Nussle, Kluthe, Riva and their co-workers.[22, 91, 101] Kluthe and Riebow[108] have demonstrated excessive gastrointestinal protein loss in experimental nephrosis produced with antirenal antibodies in the rabbit.

Intestinal Lymphangiectasia

Over the past few years a number of new syndromes have been defined in patients previously categorized as having idiopathic hypoproteinemia. The most common of these syndromes is intestinal lymphangiectasia, a disorder characterized by the early onset of massive, frequently asymmetrical edema, hypoproteinemia, lymphocytopenia, mild gastrointestinal symptoms, and generalized disorders of lymphatic channels including dilated telangiectatic lymphatic vessels of the submucosa of the small bowel. Over 40 such patients with intestinal lymphangiectasia and proven gastrointestinal protein loss have been reported from a number of laboratories.[3, 9, 11, 18, 25, 28, 32, 71, 75, 88, 89, 92, 116, 125-136] Of 45 patients presenting with idiopathic hypoproteinemia at the National Institutes of Health, 20 have had this syndrome.

This is a disease that usually affects children and young adults. The mean age of onset of symptoms was 11 years and all but four of the reported patients had their first symptoms before the age of 28. The disease is usually sporadic, however, there have been at least four families where several members were affected.[127, 128, 130, 137] All of the patients with intestinal lymphangiectasia had significant edema, usually generalized, at some time during their course. Eight of the patients had markedly asymmetric edema.[11, 18, 32, 134-136] Seventeen of the 40 patients reported had chylous effusions.[11, 18, 32, 89, 92, 127-129] Three of the patients presented with blindness secondary to macular edema. Gastrointestinal symptoms were variable but in most patients relatively mild. The majority of patients but not all had intermittent diarrhea and steatorrhea. A few patients developed marked difficulty with diarrhea, extreme steatorrhea, nausea, vomiting, and abdominal pain.

The major laboratory findings were related to the low serum proteins. There was extreme reduction of the albumin, 7-S-γ-globulin, and IgG-globulin in these patients, a moderate reduction of transferrin, ceruloplasmin and γ-macroglobulin, and normal levels of fibrinogen and α_2-macroglobulin.[135] These patients as a group had the most severe gastrointestinal protein loss. The mean survival half-time for albumin,[9, 11, 32] γ-globulin,[9, 67, 68] γ-macroglobulin,[69] and ceruloplasmin[14] was less than 25% of the normal, indicating loss into the gastrointestinal tract comparable in magnitude to severe nephrosis. The synthetic rate for albumin, γ-globulin, and ceruloplasmin was normal or slightly increased. The cholesterol was normal or low. A mild anemia was rarely encountered[75, 128] in patients with intestinal lymphangiectasia. Lymphocytopenia was an almost universal

accompaniment of this syndrome. The mean lymphocyte concentration in 20 such subjects was 600 per mm^3 as compared to 1500 to 4000 per mm^3 in control subjects. A comparable lymphocytopenia is seen with other disorders of gastrointestinal lymphatics such as Whipple's disease, constrictive pericarditis and, to a lesser extent, regional enteritis. Hypocalcemia sufficient to produce tetany has been noted in three patients.[75, 130]

Although each of the patients had significant hypogammaglobulinemia, they were able to make antibodies quite well in response to antigenic challenge. In general these patients have had abnormalities of the delayed type response and have been much less reactive to skin test antigens such as mumps or monilia than unaffected persons. In the three patients studied, heterologous skin grafts have survived for over 5 months (W. L. Strober, R. D. Wochner, P. Carbone, and T. A. Waldmann, *unpublished observations*).

The patients have usually had only moderate impairment of gastrointestinal absorption. The 4-day fecal fat output was below 7% of the ingested fat in five patients, from 7 to 10% in nine, and above 10% in nine of the patients. The fecal nitrogen and the carbohydrate absorption tests, including glucose and xylose tolerance tests, were within normal limits in most of the patients studied. Roentgenograms of the gastrointestinal tract were completely negative in four patients, showed mild mucosal edema of the small bowel in 15 patients, and showed significant sedimentation and puddling of the barium in the remaining four patients.[25, 32]

On biopsy of the jejunal mucosa the hallmark lesion of the disease is revealed; it is a dilation and telangectasia of the lymphatic vessels of the submucosa and serosa (fig. 3). Frequently these grossly dilated lymphatic vessels distort the individual villi, however, in the majority of cases there is no villous atrophy and the microvilli have been shown to be normal. The dilated lymphatic channels frequently contain foamy lipophages. The affected portions of the small bowel seen at laparotomy or autopsy are edematous and have dilated serosal lymphatic vessels. The majority of the patients have a red-brown pigmentation of the distal small bowel. The brown pigmentation has been shown to be a lipochrome pigment localized primarily to the external muscularis layer similar to that seen with other gastrointestinal disorders. There is significant evidence to suggest that the disorder of lymphatic channels is not limited to the gastrointestinal tract in patients with this syndrome. Seventeen of the patients had chylous effusions and five had markedly asymmetrical edema even following albumin infusions. Lymphangiograms performed on these patients have shown significant hypoplasia of the peripheral lymphatics with dermal backflow similar to that seen in lymphedema.[129, 136, 138] In some of the patients there was partial obstruction or absence of the thoracic duct[75, 129, 136] and, in one patient who had congenital chylous ascites, absence of periaortic abdominal lymph nodes.[129] In three studies[75, 91, 92] lymphangiogram dye injected into the foot refluxed from the area of the cysterna chyli into the mesenteric lymphatics and entered the bowel lumen.

The pathogenesis of the lymphatic abnormalities in these patients remains obscure. A congenital malformation is the most likely explanation of this disorder in those patients with an onset at birth and with a familial history of hypoproteinemia and chylous effusions. In other cases an acquired defect secondary to retroperitoneal fibrosis, pancreatitis, or other causes may be present. It is especially important to look for other disorders such as constrictive pericarditis that may present with a similar clinical, laboratory, and histological pattern.

The pathogenesis of the hypoproteinemia in some of these patients with intestinal lymphangiectasia would appear to be the rupture of the dilated lymphatic vessels with consequent discharge of their contents into the bowel lumen. Such discharge of lymph into the bowel lumen has been demonstrated in some cases with lymphangiography[75, 91, 92, 136] and in others by the demonstration of lymph in the gastrointestinal lumen using intubation.[92, 130] In other cases it has been thought that protein exuding from the intestinal capillaries enter the lumen through an intact epithelium when

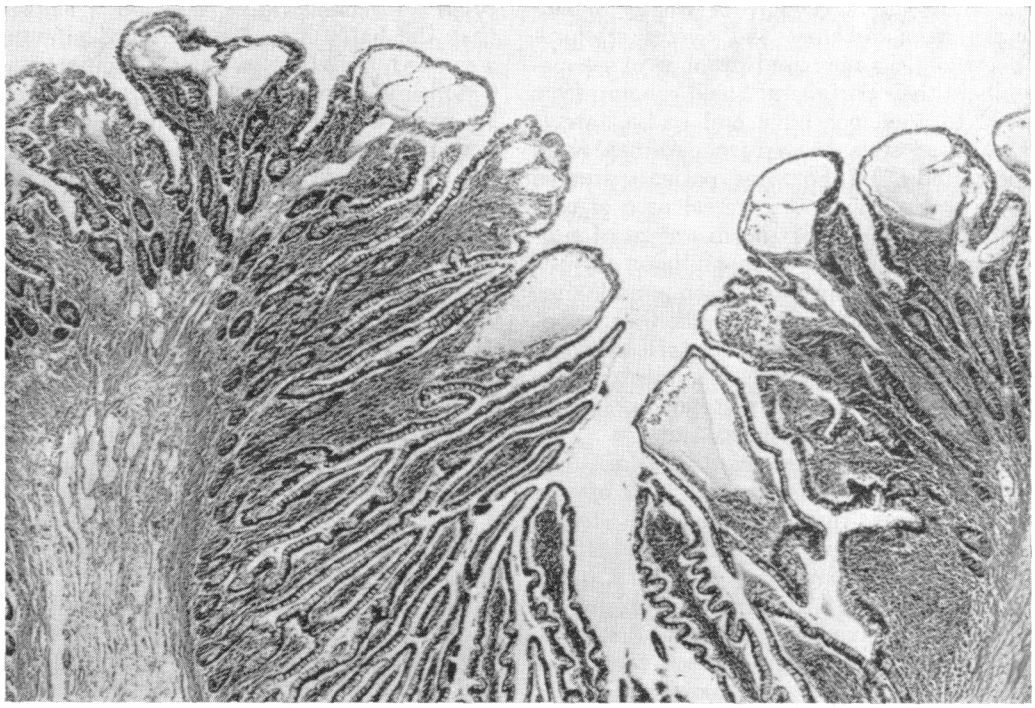

FIG. 3. Laparotomy specimen of small bowel from a patient with intestinal lymphangiectasia demonstrating dilated submucosal lymphatic channels at the tips of the villi.

the mesentery lymphatics are obstructed and cannot fulfill their normal function.

As noted below, although there is no satisfactory treatment for all patients with intestinal lymphangiectasia, two patients have had a successful resection of a localized lesion within the gastrointestinal tract[9, 116] and a number of patients have responded to a low fat diet.[9, 130, 133, 134]

Protein-Losing Enteropathy Secondary to Gastrointestinal Allergy

Six infants have been described with a syndrome of edema most marked in the periorbital area, iron deficiency anemia, eosinophilia, hypoalbuminemia, hypogammaglobulinemia, growth retardation, and typical features of allergy.[71, 136] The patients had a normal or increased rate of albumin synthesis but they had a markedly shortened albumin survival half-time of 2.8 to 3.5 days and excessive fecal excretion of I^{131}-polyvinylpyrrolidone and chromium^{51}-albumin following intravenous administration of these labeled macromolecules. The gastrointestinal symptoms were mild in these cases, limited to occasional diarrhea and, in some cases, vomiting following ingestion of milk. None of the patients had steatorrhea or an abnormal xylose tolerance test. The X-rays of the small bowel were either normal or showed mucosal edema. The stools were persistently positive for occult blood and were loaded with Charcot-Leyden crystals. No gastrointestinal parasites could be demonstrated. Biopsies of the small bowel were normal in five of the patients other than an increase in the eosinophils in the submucosa. In the sixth patient there was some mild villous atrophy. Following administration of oral iron the hemoglobin returned to normal but there was no effect on the eosinophilia or hypoproteinemia. A number of factors suggested that gastrointestinal allergy was the major factor in the pathogenesis of the excessive gastrointestinal protein loss. The patients had a strong familial history of allergy and

had other manifestations of allergy including eczema, asthma, and allergic rhinitis. They had an increased number of eosinophils in their peripheral blood ranging from 2000 to 5000 per mm^3 and had Charcot-Leyden crystals derived from eosinophils in their stools. In the three patients studied there was a complete reversal or a significant amelioration of the disorders of protein metabolism and eosinophilia on a hypoallergenic diet, specifically on a milk-free diet. On reintroduction of milk the gastrointestinal protein loss returned. In the three patients studied there was a return to or toward normal protein metabolism following corticosteroid administration.

These patients present clinical features quite similar to those in about 30 infants reported from five centers with hypoferremic, hypocupremic anemia and hypoproteinemia in infancy.[139-143] These patients appear to present a complex problem encompassing a number of different disorders. In the majority of these cases there had been a prolonged period of consumption of a diet restricted to milk. In many subjects both the hypoproteinemia and anemia could be corrected by administration of a normal diet with iron and copper supplements.[139, 140] The basic disorder was felt to be multiple dietary deficiencies leading to defects of protein synthesis in these subjects. In other patients carefully studied by Wilson, Heiner, and Lahey,[4, 103, 142-144] blood loss into the gastrointestinal tract secondary to allergy to milk was demonstrated using chromium^{51}-labeled red blood cells. Serum proteins were demonstrated in the gastric secretions of these patients by immunological methods. In these subjects circulating antibodies to milk could be demonstrated in a number of cases. It is quite probable that these patients had gastrointestinal protein loss secondary to milk allergy.

Acute Transient Gastrointestinal Protein Loss

Transient hypoproteinemia lasting from 3 weeks to a few months frequently associated with anemia and eosinophilia has been reported in a number of children and adults.[32, 71, 112, 145] In general, recovery occurred before gastrointestinal protein loss could be demonstrated. Ulstrom[112] showed that the half-time of survival of albumin was shortened in two such patients using C^{14}-phenylalanine as a protein precursor. In another patient, gastrointestinal loss could be definitively demonstrated.[32] This patient, an 11-year-old boy, developed severe hypoproteinemia, edema, anemia, and eosinophilia 2 weeks after an attack of acute gastroenteritis. During the active phase of his disease, lasting 6 weeks, the results of the I^{131}-albumin turnover and PVP excretion studies indicated significant gastrointestinal protein loss. During this hypoproteinemic phase the patient had no gastrointestinal symptoms and the gastrointestinal X-rays revealed only nonspecific mucosal edema. Transient gastrointestinal protein loss has also been demonstrated in patients with acute salmonella[3] or staphylococcal gastroenteritis.[87]

Nonspecific Granulomatous Disease Involving the Small Intestine and Mesentery Associated with Gastrointestinal Protein Loss

Holman et al.[9] and Schwartz and Jarnum[11] described several patients with gastrointestinal protein loss who were found to have nonspecific granulomatous lesions involving the jejunum. Local lymphatic obstruction was sometimes present. The diagnoses of sarcoidosis, tuberculosis, regional enteritis, and mesenteric neoplasm were considered but could not be established. The basic etiology of the granulomatous disease in these patients has not been defined. It should be noted that in addition to these disorders that have been defined, a number of patients present with severe gastrointestinal protein loss with disorders that cannot be classified into any of the well known gastrointestinal diseases. These patients present a challenge for future work directed toward discovering new syndromes involving the gastrointestinal tract.

Experimental Production of Gastrointestinal Protein Loss in Animals

Gastrointestinal protein loss has been demonstrated in rats and mice following

total body radiation,[104-107] and intraperitoneal administration of nitrogen mustard.[104] Excessive gastrointestinal protein loss has also been produced by the production of experimental pericarditis with injections of colloidion into the pericardium,[109] by the production of a fistula between the thoracic duct and the esophagus,[146] and by implanting rat bone marrow in X-irradiated mice.[147] These experimental models may aid in understanding the pathophysiology of loss of proteins into the gastrointestinal tract and may aid in the development of agents to protect the gastrointestinal tract from the effects of cancer chemotherapeutic agents and radiation.

Therapy of Gastrointestinal Protein Loss

Since excessive gastrointestinal protein loss is not a single disease entity, the therapy depends on the identification of the underlying disorder and on the adequacy of the therapy available. Remission of gastrointestinal protein loss has followed surgical resection of various localized lesions of the gastrointestinal tract including gastric polyps,[79] gastric carcinoma,[11] an eosinophilic granuloma of the stomach,[148] giant hypertrophy of the gastric mucosa,[11, 46] congenital jejunal stenosis,[18] localized granulomatous process of the ileum in a patient with agammaglobulinemia,[9] colonic carcinoma,[78] and in two cases the resection of a localized segment of intestinal lymphangiectasia.[9, 116] There was also a remission of excessive gastrointestinal protein loss following removal of the aganglionic segment in a patient with Hirschsprung's disease[94] and following the ligation of a lymphatic fistula from the cysterna chyli to the small bowel that occurred following an episode of pancreatitis.[91] As noted before there was a complete or partial amelioration of gastrointestinal protein loss following a pericardectomy or the repair of an intra-atrial septal defect in nine patients studied.[95, 96, 98, 115, 118] In the majority of patients with small bowel disease, however, the disorder is too diffuse for surgical therapy.

Corticosteroids have been effective in correcting gastrointestinal protein loss in some patients with ulcerative colitis,[46] regional ileitis,[149] iliocolitis associated with agammaglobulinemia,[100] and allergic gastroenteropathy.[136, 150] Therapy with antibiotics has been effective in rapidly reversing the gastrointestinal protein loss associated with Whipple's lipodystrophy[76] and in a patient with chronic salmonellosis and agammaglobulinemia[100] and in one patient with lymphosarcoma involving the bowel, chlorambucil therapy was effective in returning the I^{131}-albumin turnover and PVP test to normal.[85]

There was a return to normal protein metabolism following therapy with a gluten-free diet in patients with nontropical sprue,[46, 37, 110] celiac disease,[132] and in two subjects with agammaglobulinemia and an associated spruelike syndrome.[44, 100] A hypoallergenic diet, specifically a milk-free diet, has been effective in some patients with allergic gastroenteropathy.[103, 136] When milk was reinstituted, there was a return of the gastrointestinal protein loss. A protein-free diet was shown to reverse apparent gastrointestinal protein loss in two cases.[151, 152] The hypoproteinemia recurred following the readministration of protein but not of amino acids. As noted previously, surgical resection has been an effective therapy in two patients with intestinal lymphangiectasia.[9, 116] In the majority of these subjects, however, surgical resection of the most affected lesion, corticosteroids or antibiotics have not been of value. In a few cases a significant increase in the serum protein concentration and reduction of the edema have been reported using a low fat diet.[9, 130, 133, 134] Recently Jeffries et al.[133] studied two such patients with intestinal lymphangiectasia to determine the effect of a low fat diet or the replacement of long chain triglycerides with middle chain triglycerides in the diet. The I^{131}-labeled albumin survival returned toward normal following the institution of the low fat diet. In a similar study by Holt[134] there was a comparable marked improvement of the disorder of protein metabolism when dietary long chain triglycerides were replaced by middle chain triglycerides in a patient with lymphangiectasia. It has been shown that there is a two- to threefold increase in thoracic duct flow following the administra-

tion of fat.[153] The use of a low fat diet or a diet using middle chain triglycerides that are absorbed into the portal vein rather than through the lymphatics would be expected to have its effect through a reduction of lymph flow and pressure in these patients with disordered lymphatic function.

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